Evaluation for latent tuberculosis

What should I do about this positive skin test?

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Tsukayama
A patient presents with a 12 mm TST and CXR shows fibrotic changes in the RUL interpreted as consistent with old tuberculosis. The patient has never been treated for tuberculosis. Sputum AFB smears are obtained and are negative. The patient is asymptomatic. At this point you should:

A. Wait for the AFB culture results which will take 6 weeks

B. Treat for latent infection

C. Treat for active disease

D. Tell the patient you don’t know what to do and ask her what she would like to do
Teaching Points

• Negative AFB smears imply low risk of transmission but do not rule out active disease

• A CXR cannot distinguish inactive from active disease

• Negative cultures and stable CXR in an asymptomatic patient are sufficient to rule out active pulmonary disease.
Your patient has a TST of 8 mm. What is the next test you should order?

A. repeat the TST in one week
B. CXR
C. No further testing is needed. This is a negative test.
D. No further testing is needed. This is a positive TST. Isoniazid should be started.
Objectives of Evaluation

• Determine whether the test is a true positive
• Rule out active disease
• Treat latent infection

Do not treat active infection with one drug
Basic Evaluation

- History
- Physical
- TST or IGRA
- CXR
- Sputum AFB
Extended Evaluation

- Other imaging (CT scan)
- Histology and AFB culture from other sites
- Response to empiric treatment
H&P

• Exposure to tuberculosis
• Progression from infection to active disease
• Risk of adverse side effects of treatment
• Symptoms suggestive of tuberculosis
• Physical examination findings suspicious for tuberculosis
Evaluation for tuberculosis

- History
  - Risk for infection or progression to disease
  - Contact of recent case
  - Family history of TB
  - Liver and kidney function
  - Medications

- Symptom Review
  - Fever, fatigue, night sweats, weight loss
  - Cough, chest pain, hemoptysis
  - Other sites

- Physical Exam
  - Eyes
  - Lymph nodes
  - Chest
  - Liver
  - Neurological

- Risk for infection
- Foreign born
- Frequent/prolonged visits to high-risk areas
- Contact of recent case
- Exposure in prison, homeless shelter, nursing home
- Risk for progression to disease
- HIV infection
- Children under 5 years old
- Immunosuppressive medication
- TB infection within 2 years
- inadequately treated prior TB
- diabetes mellitus, smoking, renal failure, malignancy
Tuberculin Skin Test (TST)

• Standard test for diagnosing TB infection
• May not react for 8-10 weeks
• Cannot distinguish latent from active
• Negative test does not rule out active disease
• Booster effect from old TB infection or BCG
The advantage of the interferon-gamma release assay over the tuberculin skin test is that it:

A. Will become positive within 2 weeks of exposure

B. Can distinguish between latent and active TB

C. Does not have a false-positive result with BCG

D. Will revert to negative after treatment
Table 7. Criteria for tuberculin positivity, by risk group

<table>
<thead>
<tr>
<th>Reaction ≥5 mm of induration</th>
<th>Reaction ≥10 mm of induration</th>
<th>Reaction ≥15 mm of induration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus (HIV)-positive persons</td>
<td>Recent immigrants (i.e., within the last 5 yr) from high prevalence countries</td>
<td>Persons with no risk factors for TB</td>
</tr>
<tr>
<td>Recent contacts of tuberculosis (TB) case patients</td>
<td>Injection drug users</td>
<td></td>
</tr>
<tr>
<td>Fibrotic changes on chest radiograph consistent with prior TB</td>
<td>Residents and employees of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters</td>
<td></td>
</tr>
<tr>
<td>Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/d of prednisone for 1 mo or more)*</td>
<td>Mycobacteriology laboratory personnel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunooileal bypass</td>
<td>Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk</td>
</tr>
</tbody>
</table>

* Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

† For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

# Tuberculin Skin Test

<table>
<thead>
<tr>
<th>False-positive</th>
<th>False-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non-tuberculous mycobacteria</td>
<td>• Active tuberculosis</td>
</tr>
<tr>
<td>• BCG</td>
<td>• Cell-mediated immunosuppression by</td>
</tr>
<tr>
<td>• Improper reading</td>
<td>• disease</td>
</tr>
<tr>
<td></td>
<td>• medication</td>
</tr>
<tr>
<td></td>
<td>• extremes of age</td>
</tr>
<tr>
<td></td>
<td>• Some chronic diseases (A)</td>
</tr>
<tr>
<td></td>
<td>• Severe or febrile illness (B)</td>
</tr>
<tr>
<td></td>
<td>• &lt;1 month after</td>
</tr>
<tr>
<td></td>
<td>• live virus vaccine (C)</td>
</tr>
<tr>
<td></td>
<td>• some illnesses (D)</td>
</tr>
<tr>
<td></td>
<td>• Improper placement or reading</td>
</tr>
</tbody>
</table>

A. Chronic renal failure, cirrhosis, malnutrition, sarcoidosis
B. Includes tuberculosis
C. MMR, Polio, Yellow Fever
D. Measles, mumps, rubella, varicella, mononcleosis, typhoid, brucellosis, influenza
Prevalence of LTBI: US Residents

Horsburgh, Rubin. NEJM 364:1441, 2011

<table>
<thead>
<tr>
<th>Group and Study</th>
<th>Expected Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign-born persons</td>
<td>18.7 (13.5–25.2)</td>
</tr>
<tr>
<td>Bennett et al.⁴</td>
<td></td>
</tr>
<tr>
<td>Close contacts of persons with infectious tuberculosis †</td>
<td>37.1 (35.7–38.5)</td>
</tr>
<tr>
<td>Marks et al.⁸</td>
<td></td>
</tr>
<tr>
<td>Homeless persons</td>
<td>12.8 (12.2–13.5)</td>
</tr>
<tr>
<td>Kong et al.⁹</td>
<td></td>
</tr>
<tr>
<td>Moss et al.¹⁰</td>
<td>32.4 (30.5–34.4)</td>
</tr>
<tr>
<td>Injection-drug users</td>
<td></td>
</tr>
<tr>
<td>Riley et al.¹¹</td>
<td>16.1 (12.5–22.4)</td>
</tr>
<tr>
<td>Grimes et al.¹²</td>
<td>27.7 (19.3–37.5)</td>
</tr>
<tr>
<td>Brassard et al.¹³</td>
<td>22.4 (17.7–28.5)</td>
</tr>
<tr>
<td>Salomon et al.¹⁴</td>
<td>14.0 (11.4–17.1)</td>
</tr>
<tr>
<td>Prisoners</td>
<td></td>
</tr>
<tr>
<td>Lobato et al.¹⁵</td>
<td>17.0 (16.8–17.1)</td>
</tr>
<tr>
<td>U.S.-born, no other risk</td>
<td></td>
</tr>
<tr>
<td>Bennett et al.⁴</td>
<td>1.8 (1.4–2.1)</td>
</tr>
</tbody>
</table>

* See the Supplementary Appendix for the definition of a positive test result. CI denotes confidence interval. † This group was not strictly defined but is generally considered to consist of members of the household of an infected person.
### Table 2. Common Risk Factors for Increased Likelihood of Progression from Latent Tuberculosis Infection to Active Disease.*

<table>
<thead>
<tr>
<th>Risk Factor and Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced, untreated HIV infection</td>
<td>9.9 (8.7–11)</td>
</tr>
<tr>
<td>Moss et al.^{10}</td>
<td></td>
</tr>
<tr>
<td>Pablos-Méndez et al.^{16}</td>
<td>9.5 (3.6–25)</td>
</tr>
<tr>
<td>Close contact with a person with infectious tuberculosis†</td>
<td>6.1 (5.5–6.8)</td>
</tr>
<tr>
<td>Ferebee^{17}</td>
<td></td>
</tr>
<tr>
<td>Radiographic evidence of old, healed tuberculosis that was not treated</td>
<td>5.2 (3.4–8.0)</td>
</tr>
<tr>
<td>Ferebee^{17}</td>
<td></td>
</tr>
<tr>
<td>Treatment with ≥15 mg of prednisone per day‡</td>
<td>2.8 (1.7–4.6)</td>
</tr>
<tr>
<td>Jick et al.^{18}</td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>2.4 (2.1–2.8)</td>
</tr>
<tr>
<td>Pablos-Méndez et al.^{16}</td>
<td></td>
</tr>
<tr>
<td>Treatment with TNF-α inhibitor</td>
<td>2.0 (1.1–3.5)</td>
</tr>
<tr>
<td>Asling et al.^{19}</td>
<td></td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td>1.7 (1.5–2.2)</td>
</tr>
<tr>
<td>Pablos-Méndez et al.^{16}</td>
<td></td>
</tr>
<tr>
<td>Weight ≥10% below normal</td>
<td>1.6 (1.1–2.2)</td>
</tr>
<tr>
<td>Palmer et al.^{20}</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.5 (1.1–2.2)</td>
</tr>
<tr>
<td>Bates et al.^{21}</td>
<td></td>
</tr>
</tbody>
</table>

* Relative risk was calculated as described in Horsburgh.\(^3\) CI denotes confidence interval, HIV human immunodeficiency virus, and TNF tumor necrosis factor.

† Relative risk was calculated for the first 3 years after exposure.

‡ The drug was taken for 2 weeks or more.
Interferon gamma release assays

• Measures release of interferon gamma by lymphocytes to stimulation by specific MTB antigens- ESAT-6, CFP-10, *TB7.7*(QFT only)

• Test has positive and negative controls

• No cross-reactivity with BCG or Mycobacterium avium-intracellulare

• Cross-reactive with M. bovis, M. kansasii, M. marinum, M. szulgai

• Blood test, requires only one visit

• Two approved tests- Quantiferon and T-Spot
CDC Guidelines for IGRA Use 2010

• “QFT-G may be used in place of (but not in addition to) a TST in all situations in which CDC recommends TST as an aid in diagnosing MTB infections…”

Performance of IGRA may be decreased in immunocompromised patients, including children less than 5 years old

MMWR 59 (RR-5), 2010
2010 CDC Recommendations for IGRA

MMWR 59 (RR-5), 2010

• IGRA preferred
  • likelihood that TST will not completed
  • Patient has received BCG vaccine

• TST preferred
  • Children less than 5 years old

• No preference
  • Contact investigation
  • Regular screening

• Both TST and IGRA can be considered
  • High risk for TB infection or disease
  • After positive TST in patient with BCG vaccination
  • Indeterminate or borderline IGRA
CXR

• Do for all cases in latent tuberculosis evaluation

• Findings suggestive of TB include upper lobe infiltrates, pleural effusion, hilar adenopathy

• Cavitary lesions imply higher risk of transmission to others

• Cannot rule out active disease with a CXR
AFB Smear

- False-positive result from nontuberculous mycobacteria
- False negative in up to 50% of culture-positive cases
- Only test available for diagnosing TB in many parts of the world
- New test- Nucleic acid amplification probe can identify Mycobacterium tuberculosis in one day, best in smear-positive cases
Evaluation of Tuberculosis

Management Options

• Obtain or repeat diagnostic studies
• Wait for final culture results
• Work up for extrapulmonary tuberculosis
  ◦ No further testing or treatment
  ◦ Treat latent tuberculosis
  ◦ Treat active tuberculosis
    - Assess need for respiratory isolation
    - Assess need for evaluation of vulnerable contacts
What is the shortest duration of effective treatment for latent tuberculosis?

A. 2 months
B. 3 months
C. 4 months
D. 6 months
# Latent TB Treatment

## Table 1. LTBI Treatment Regimens

<table>
<thead>
<tr>
<th>Drugs/Regimen</th>
<th>Interval</th>
<th>Minimum # of doses for treatment completion</th>
<th>Rating for HIV-negative persons</th>
<th>Rating for HIV-positive persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid/9 month</td>
<td>Daily</td>
<td>270</td>
<td>A (II)</td>
<td>A (II)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly</td>
<td>76</td>
<td>B (II)</td>
<td>B (II)</td>
</tr>
<tr>
<td>Isoniazid/6 month</td>
<td>Daily</td>
<td>180</td>
<td>B (I)</td>
<td>C (I)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly</td>
<td>52</td>
<td>B (II)</td>
<td>C (II)</td>
</tr>
<tr>
<td>Rifampin/4 month</td>
<td>Daily</td>
<td>120</td>
<td>B (II)</td>
<td>B (III)</td>
</tr>
<tr>
<td>Rifampin and Pyrazinamide/2 months</td>
<td>Daily</td>
<td>Due to the reports of severe liver injury and deaths, the combination of rifampin and pyrazinamide should generally not be offered for the treatment of LTBI.</td>
<td>D (II)</td>
<td>D (II)</td>
</tr>
</tbody>
</table>
New: Once weekly LTBI treatment

- rifapentine 900 mg and isoniazid 900 mg
- total duration of treatment: 12 doses
- Recommended for health persons $\geq 12$ years
- Preferred regimen for children 2-11 is INH alone
- NOT recommended for
  - Children $<2$ years old
  - HIV patients on anti-retroviral therapy
  - Pregnant women
  - Resistance to INH or RIF
Once weekly LTBI treatment

- Directly observed therapy is recommended
- Monthly clinical monitoring
- Consider in persons unlikely to complete 9 months of therapy
- Case-by-case consideration in children ages 2-11, patients with underlying conditions associated with tuberculosis.